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Hydrolysis Rate Constants for Enhancing Property-Reactivity Relationships

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Hydrolysis Rate Constants for Enhancing Property-Reactivity Relationships

by

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Rate constants for hydrolysis in water of ten classes of organic compounds are examined with the objective of establishing new, or expanding existing, property-reactivity correlations. These relationships then can be used to predict the environmental hydrolysis of chemicals that have similar molecular structure. The compound classes covered by this report include aliphatic and aromatic carboxylate esters, alkyl and aromatic halides, amides, carbamates, epoxides, nitriles, phosphate esters, alkylating agents, halogenated ethers, and oxidized sulfur compounds. Three predictive techniques (the first based on empirical correlations with derived constants, the second using infrared spectra, and the third relying on fundamental calculations requiring only chemical structure) were used to predict and compare hydrolysis rate constants for simple alkyl esters. The predicted rate constants were generally within a factor of two of each other and the laboratory-determined values.

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FOREWORD

As environmental controls become more expensive and penalties for judgement errors become more severe, environmental management requires more precise assessment tools based on greater knowledge of relevant phenomena. As a part of this Laboratory's research on occurrence, movement, transformation, impact, and control of chemical contaminants, the Measurements Branch determines the occurrence of unsuspected organic pollutants in the aquatic environment and develops and applies techniques to measure physical, chemical, and microbial transformation and equilibrium constants for use in assessment models and for development of property-reactivity correlations.

In response to the land banning provision of the 1984 Hazardous and Solid Waste Amendments to PL 98-616, the Resource Conservation and Recovery Act (RCRA), a mathematical model was developed to estimate potential groundwater contamination from chemicals placed in land disposal sites. Application of the model requires as input the hydrolysis rate constant(s) for chemical(s) of concern. Measured hydrolysis rate constants and the development of property-reactivity correlations to predict them for similar chemicals are discussed relative to their potential application to new chemicals being considered by EPA's Office of Solid Waste for regulation.

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ABSTRACT

This report examines the rate constants for hydrolysis in water of 10 classes of organic compounds with the objective of establishing new or expanding existing property-reactivity correlations. These relationships can then be used to predict the environmental hydrolysis fate of chemicals that have similar molecular structure. The compound classes covered by this report include: aliphatic and aromatic carboxylate esters, alkyl and aromatic halides, amides, carbamates, epoxides, nitriles, phosphate esters, alkylating agents, halogenated ethers, and oxidized sulfur compounds. Three predictive techniques (one based on empirical correlations with derived constants, another using infrared spectra and a third relying on fundamental calculations requiring only chemical structure) were used to predict and compare hydrolysis rate constants for simple alkyl esters. The predicted rate constants were generally within a factor of two of each other and the laboratory-determined values.

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Hydrolysis Rate Constants for Enhancing Property Reactivity Relationships

1.0 Introduction

Each year more than 1000 new chemicals are introduced into commerce and thus into the environment worldwide. Regulators and scientists need reliable data on the persistence, mobility, toxicity and possible risk to humans or the ecosystem associated with these new chemicals as well as the more than 65,000 currently in use (1). The possible persistence of these chemicals and accompanying risk of exposure to humans and other species of concern has resulted in a demand on regulators to provide effective techniques for quantifying their mobility and fate.

As part of the effort to evaluate potential mobility and fate associated with chemical constituents of wastes under consideration for land disposal, EPA's Office of Solid Waste (OSW) uses a relatively simple model to estimate potential groundwater contamination at specified withdrawal points in proximity to a landfill. This model calculates horizontal chemical movement in the aquifer based on advection, dispersion, sorption and transformation. Hydrolysis is the only transformation process specifically considered at this time.

To apply this model to chemicals of interest to OSW, hydrolysis rate constants for 98 chemicals were previously obtained either from literature sources or laboratory

determinations (2-4) using protocols developed at ERL-Athens (5).

The objective of this report was to examine the rate data presented in references 2-4 and organize them by compound class, with the goal of either enhancing existing property-reactivity correlations (PRCs) or developing new PRCs if sufficient data have been generated for a particular class of chemicals. These correlations then can be applied to new chemicals in wastes being considered by OSW for regulation.

2.0 Property Reactivity Correlations (PRCs) and Prediction Programs

The use of PRCs for predicting rate and equilibrium constants for organic reactions is well established (6). Pharmaceutical and pesticide manufacturers routinely use historical data on existing compounds in designing new products to either increase or decrease potency and/or persistence while decreasing or eliminating unwanted side effects. Any chemical released to the environment is subjected to a wide variety of conditions that can transform it to a different product. PRCs offer a means for estimating kinetic constants for important transformation processes such as hydrolysis, photolysis, and redox reactions.

For example, a symposium, "Structure-Activity Relationships in Environmental Toxicology and Chemistry" was part of the American Chemical Society Meeting April 6-8,1987, in Denver, Colorado. The symposium topics included SARs to estimate rate constants for oxidation by $HO^{\bullet}$ radicals in the troposphere and peroxy radical and singlet oxygen reactions in surface waters,

and to estimate salinity constants for ligands and selected metal ions. Several SARs correlated molecular structure with toxicity to aquatic organisms.

The reliability of any PRC/SAR is directly related to the accuracy of data input and to how well the selected data represent the particular process. Most existing PRCs are empirical correlations (based on derived measures of the polar and/or steric effects of compound structure) that predict new kinetic constants only for reaction pathways for which data exist for similar transformations. Using this approach, Drossman, Johnson and Mill developed SARs for base-promoted hydrolysis of esters and carbamates using σ^* and E_s values for the compounds of interest (7).

Two approaches that are less dependent on measured kinetic data are being developed at ERL-Athens. Collette (8) is developing a method for predicting environmental fate constants of chemicals based on their infrared spectra. Even though many reactivity parameters may be amenable to this approach, to date, only alkaline hydrolysis of organic esters has been considered in depth. Karickhoff et al. (9) is developing a prototype computer program SPARC (SPARC Performs Automated Reasoning in Chemistry) that uses computational alogrithms based on fundamental chemical structure theory. This allows estimation of values for a broad variety of reactivity parameters both kinetic and equilibrium: Uv light absorption, pKa, and various reaction rate constants, or any parameters that depend on molecular structure. The agreement of the alkaline hydrolysis rate constants for carboxylate esters

calculated by all of the above methods as well as determined in the laboratory will be discussed in more detail later.

3.0 Hydrolysis Background

Hydrolysis of organic compounds refers to reaction of the compound with water in which bonds are broken and new bonds with HO- and H- are formed. A common example is the reaction of an alkyl halide with water resulting in the loss of halide ion (-X):

$$RX + HOH \longrightarrow ROH + HX \text{ (or } H^+, X^-)$$

The rate of the reaction may be promoted by the hydronium ion (H^+, or H_3O^+) or the hydroxyl ion (OH^-). The former is referred to as specific acid catalysis and the latter as specific base catalysis. These two processes together with the neutral water reaction were the only mechanisms considered in references 2-5.

Some chemicals show a pH-dependent elimination reaction:

$$-\overset{H}{\underset{|}{C}}-\overset{X}{\underset{|}{C}}- \xrightarrow[OH^-]{H^+ \text{ or}} C = C + HX$$

For the hydrolysis rate constants reported in references 2-5, only the disappearance of substrate was monitored with no attempts to identify mechanisms.

If all processes referred to as hydrolysis are included, the rate of hydrolysis is given by the equation,

$$-\frac{d[C]}{dt} = k_h[C] = k_A[H^+][C] + k_B[OH^-][C] + k_N'[H_2O][C] \qquad (1)$$

where [C] is the concentration of reactant and k_h is the observed pseudo-first-order rate constant at a specific pH and temperature, k_A, k_B, and k_N' are second-order rate constants for the acid, base and neutral promoted processes, respectively. The water concentration is essentially not depleted by the reaction and is much greater than [C], thus $k_N'[H_2O]$ is a constant (k_N), the pseudo-first order neutral rate constant.

Equation 1 assumes each individual rate process is first order in substrate, thus k_h can be defined as:

$$k_h = k_A[H+] + k_B[OH^-] + k_N \qquad (2)$$

Equation 1 then becomes simply,

$$-\frac{d[C]}{dt} = k_h[C] \qquad (3)$$

which integrates to

$$[C]_t = [C]_o \exp(-k_h t) \qquad (4)$$

or

$$\ln \frac{[C]_t}{[C]_o} = k_h t \qquad (5)$$

Equation 5 allows calculation of the concentration of a reactant at any time (t). Specifically, when $[C]_t = \frac{1}{2}[C]_o$, equation 5 reduces to:

$$t = t_{\frac{1}{2}} = \frac{\ln \frac{100}{50}}{k_h} = \frac{\ln 2}{k_h} = \frac{0.693}{k_h} \qquad (6)$$

For many chemicals, hydrolysis can be the dominant pathway for degradation in the environment. Functional groups that are potentially susceptible to hydrolysis are:

1. Aliphatic and aromatic carboxylate esters
2. Alkyl and aromatic halides
3. Amides
4. Carbamates
5. Epoxides
6. Nitriles
7. Phosphate esters
8. Alkylating agents
9. Halogenated ethers
10. Oxidized sulfur compounds

Tables 1 through 10 contain hydrolysis rate constant data and half-lives for chemicals in the above classes at pH 7 in aqueous solution at 25°C. The corresponding figures contain structures of selected chemicals in these classes. The data in Tables 1 through 10 were either reported in references 2-4 or extracted from the indicated references for comparison purposes. For data generated at other temperatures, the rate constants were extrapolated to 25°C using either the experimentally-determined activation energies for each chemical, or an assumed activation energy (E_a) of 20 kcal/mol for each path (acid, neutral, or base hydrolysis). Since the majority of compounds have measured E_a

values in the range of 15 to 25 kcal/mol, the assumption of 20 kcal/mol for E_a generally introduce less than an order of magnitude error in the extrapolated rate constant.

Mabey and Mill (10) completed a critical review of the hydrolysis of organic compounds in water under environmental conditions. Hydrolysis rate constant values from Mabey and Mill are herein used, where available, for comparison purposes.

4.0 Hydrolysis Rate Constants and Half-Lives at pH 7 and 25°C

4.1 Aliphatic and Aromatic Carboxylate Esters

Table 1 summarizes data for hydrolysis of aliphatic and aromatic esters at 25°C and pH 7. For these compounds, hydrolysis at pH 7 is dominated by hydroxide ion for simple alkyl and aromatic esters (10). Thus, the values of k_B yield a reliable calculation of k_h and half-lives at pH 7. For more structurally complex esters and esters with substitutents that reduce the electron density of the carbonyl carbon (α-halogenated) neutral hydrolysis (k_N) will be competitive at pH 7. The general rule is that methyl esters are twice as reactive as other n-alkyl esters and branching on the α-carbon on either side of the carboxylate group will retard hydrolysis by factors of three to ten (7).

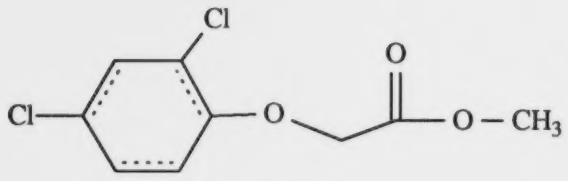
The above effects (i.e., the reduction of electron density by the phenyl substituent and methyl versus ethyl ester) are evident in the factor of eight increase in 2,4-D methyl ester hydrolysis rate compared to ethyl methoxyacetate. The 2,4-D methyl ester was used as a standard reference compound and the reported rate constant is the mean of 27 determinations. Lasiocarpine and reserpine are structurally complex molecules that have two

hydrolyzable groups (labeled 1 and 2 in Figure 1). Site 1 in lasiocarpine is structurally similar to methyl methacrylate and site 2 is structurally similar to ethyl glycolate. Branching on the α-carbon at site 2 (potentially the most easily hydrolyzed) retards hydrolysis to the extent that disappearance is dominated by neutral hydrolysis. Similarly, in reserpine, branching on the acyl carbon at site 1 (compare with methyl acetate) retards hydrolysis by hydroxide ion to the extent that neutral hydrolysis is again dominant at pH 7. Addition of a methyl group to the α-carbon of the acyl group of methyl acrylate (11) to form methyl methacrylate decreases the k_B by a factor of two. The small k_B for di-n-octylphthalate is consistent with increasing chain length in the alcohol group (8).

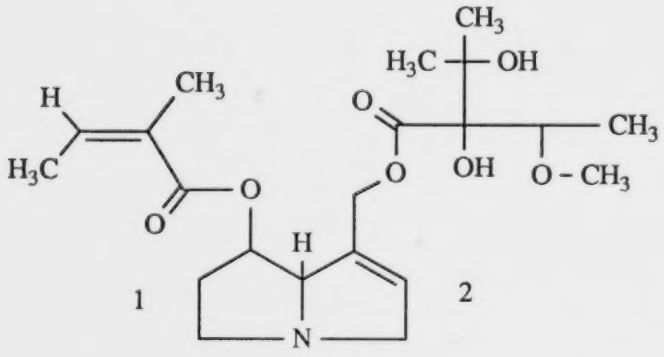
TABLE 1. ALIPHATIC AND AROMATIC CARBOXYLATE ESTERS

CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
1928-38-7	2,4-D Methyl ester			41,000 ± 5,000	7d	4
3938-96-3	Ethyl methoxyacetate			4968	58d	7
	Ethyl glycolate			3636	79d	7
303-34-4	Lasiocarpine		(4.9 ± 0.1)E-5	9.8 ± 0.1	1.6y	3
96-33-3	Methyl acrylate			406[a]	1.9y	11
79-20-9	Methyl acetate			655	1.2y	7
50-55-5	Reserpine		(4.5 ± 1.8)E-5	9.8 ± 11	1.7y	2
93-89-0	Ethyl benzoate			105	7.5y	7
80-62-6	Methyl methacrylate			200 ± 47	3.9y	3
84-66-2	Diethylphthalate			90	8.8y	8
84-74-2	Dibutylphthalate			36	22y	8
117-84-0	Di-n-Octylphthalate			7.4	107y	3

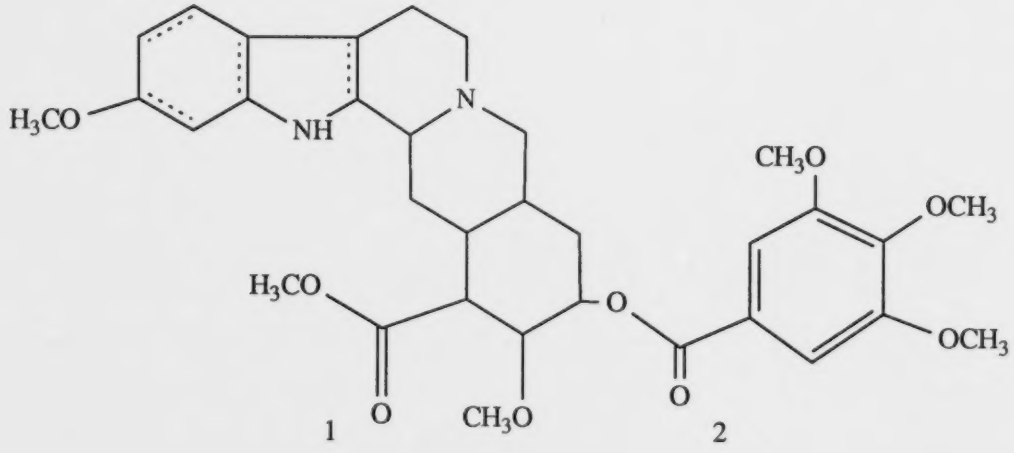
a. Assumed E_a = 20 kcal/mol in extrapolating k_B from 30°C to 25°C.



2,4-D Methyl ester



Lasiocarpine



Reserpine

Figure 1. Aliphatic and Aromatic Carboxylate Esters

4.2 Alkyl and Aromatic Halides

The halogenated compounds in Table 2 range in complexity from the simple chloroethane to the multihalogenated polycyclics such as aldrin. All have in common the potential hydroxide ion or water mediated cleavage of the carbon-halogen bond to give alcohols. E2 elimination to give olefins and hydrogen halides, although not true hydrolysis, can occur in water and may be enhanced by increasing hydroxide ion concentration and temperature. Elimination is treated as hydrolysis in the present text. Multifunctional halogenated chemicals (such as halogenated ethers and nitriles) are also included in Table 2 because the point of attack for these compounds is also the carbon-halogen bond. Table 2 is subdivided into the four groups: chlorinated alkyls, brominated alkyls, bifunctional chloroalkanes, and polycyclic and aromatic hydrocarbons.

A. Chlorinated Alkyls (Table 2, Figure 2)

Allyl halides such as allyl chloride are known to hydrolyze rapidly by a neutral mechanism. Both chlorines in cis and trans-1,4-dichloro-2-butene (DCB) are allylic. Therefore, because this compound has two equally reactive groups per molecule, the disappearance rate constant for the DCBs should be larger than that for allyl chloride. It is, in fact, larger by a factor of 20. Pentachlorocyclohexene (PCCH) has a chlorine on the gamma carbon of the allyl fragment. The gamma chlorine on PCCH retards formation of the carbonium ion and subsequent reaction of the allylic chlorine by an order of magnitude (half-life = 2.1 years). Benzyl chloride was used as a standard reference compound in the laboratory determination of hydrolysis rate constants for selected

justified but probably preferred to the uniform assumption of a 20 kcal/mole activation energy.

A second gem-dihalide (p,p'-DDD) undergoes slow neutral hydrolysis (half-life 28 years), apparently due to steric/electronic interferences from the two p-chlorinated phenyls on the α-carbon (Figure 2). Jeffers reported that a gem-dihalide with a H-atom on the gem-substituted carbon (1,1-DCA) undergoes slow neutral hydrolysis in comparison with the perhalogenated gem-dichloride (2,2-DCP). The methyl group in 1,2-dichloropropane (1,2 DCP) increases the reactivity by a factor of five versus 1,2-dichloroethane (1,2 DCA). The third chlorine in 1,2,3-trichloropropane decreases the hydrolysis rate by a factor of three versus versus that of 1,2 DCP. The fully chlorinated hexachloroethane is almost totally resistant to hydrolysis.

B. Brominated Alkyls

The reactivity of the vicinal bromines in the three brominated alkyls studied should determine the hydrolysis disappearance rate constants. The factor of nine greater reactivity of ethylene dibromide (EDB) over 1,2-dichloroethane (Table 2 Section a) illustrates the increased susceptibility of brominated compounds to hydrolysis. Statistically, tris(2,3-dibromopropyl)phosphate (Tris) with three vicinal bromine centers should have a larger k_N than ethylene dibromide. The two k_N values are almost identical, however, which leaves alkaline hydrolysis (k_B) of the phosphate ester as the determining factor for the shorter half-life (4.4y) compared to EDB (8y). Apparently, disappearance of 1,2-dibromo-3-chloropropane (DBCP) is controlled by hydroxide-ion-mediated dehydrobromination (E2

Appendix VIII chemicals (5). The standard rate constant value in Table 2 is the average of 28 determinations and agrees well with the value of 4.6 E-2 h^{-1} in Mabey and Mill (10). Hydrolysis of benzyl chloride is similar to that of the allyl chlorides in that the rate is enhanced by the ease of formation of a reactive carbonium ion.

Jeffers (12) and Queen and Robertson (13) independently determined that gem-dihalides are unreactive to nucleophilic displacement by hydroxide ion but both measured a neutral hydrolysis rate constant (attack by water) and activation energy for 2,2-dichloropropane. Jeffers' and Queen and Robertson's k_N values are approximately a factor of 2 lower than our value (4). Our rate was determined at 45°C, however, and extrapolated to 25°C using an assumed activation energy of 20 kcal/mol. If Jeffers' average value of 25.2 kcal/mol for neutral hydrolysis of chlorinated alkyls is used to extrapolate our rate from 45°C, we obtain a value of 2.4±0.12 E-2h^{-1}, which is within experimental error of Queen and Robertson's (13) value of 2.44 E-2 h^{-1} (who reported an activation energy of 26.6 kcal/mol).

Jeffers (12) reported the hydrolysis rate constants for 18 chlorinated methanes, ethanes, ethenes, and propanes that were measured in dilute aqueous solutions within the temperature range of 0 to 180°C and at pH values from 3 to 14. The average of neutral activation energies reported by Jeffers was 25.2±2.87 kcal/mol whereas the average for 15 basic activation energies was 26.2±3.87 kcal/mol. Thus, for chlorinated alkanes when the activation energy is unknown, use of Jeffers' values to extrapolate rates to other temperatures would not only be

elimination) as evidenced by the k_s term, whereas for another similarly substituted trihaloalkyl, 1,2,3 trichloropropane (Table 2, Section a), disappearance is dominated by reaction with water (k_N). The electronegative chlorine on the β-carbon in DBCP apparently enhances elimination of HBr to make dehydrobromination the dominant pathway at pH 7.

C. Bifunctional Chloroalkanes

The halogenated alkanes in this group contain either hydroxyl, cyano, or the ether linkage as the second functional group. The two chloropropanols (1,3-DCA and 2,3-DCA) differ in reactivity by two orders of magnitude. As a first approximation, one might expect that the reactivity of 1,3-DCA should be comparable to 1,3-dichloropropane (1,3-DCP), but the observed rate constant for 1,3-DCP is closer to the value of 2,3-DCA. The enhanced reactivity of 1,3-DCA can be attributed to the 2-hydroxyl group. Electronegative substituents on the β-carbon are known to enhance reactivity of α-halogens (13). Additionally, the acid character of the hydroxyl is enhanced by the two chlorines. The oxyanion resulting from ionization of the weak acid can, through intramolecular cyclization, displace either adjacent chlorine to form epichlorohydrin, a reactive intermediate. Similar ionization and cyclization enhances the reactivity of 2-chloroethanol (2-CE) versus 1,2-dichloroethane (1,2-DCA). The 2,3-DCA contains vicinal chlorines but the hydroxyl substituent enhances reactivity by only one order of magnitude over 1,2-DCA.

The bis-dichloroethyl ether (DCE) reactivity, as expected, was similar to that of ethyl chloride. The 2-(2-chloroethoxy) ethanol (CEE) with one less reactive chlorine than DCE has a

slightly enhanced rate over DCE, again due to intramolecular oxyanion displacement of the chlorine to form the cyclic dioxane. The oxygen substituent on the α-carbon of chloromethyl methyl ether enhances reactivity by six orders of magnitude over bis-dichloroethyl ether. The ease of formation and stability of the methoxymethyl carbonium ion has been proposed to explain the enhanced reactivity of chloromethyl ethers (20) over chlorethyl ethers.

D. Polycylic and Aromatic Halogenated Hydrocarbons

The halogenated polycyclic and aromatic hydrocarbons comprise a very persistent group of chemicals in the environment. The three most reactive polycyclic compounds studied (Aldrin, Dieldrin, and Isodrin) all contain a perchlorinated gem-dichloro carbon. Dieldrin (Aldrin epoxide) also contains an epoxide oxygen, and, with two reactive centers, would be expected to have the shortest half-life. Apparently hydrolysis of the epoxide is stericly hindered and the orientation of the cyclic ring is such that hydrolysis of the gem-dihalide also is retarded in comparison to 1,2-DCP.

Structural orientation is also the reason that the cis isomer of chlordane is more susceptible to hydroxide-ion-mediated dehydrohalogenation. The 1-exo, 2-exo orientation of the chlorine atoms in cis-chlordane facilitates the E2 elimination of HCl. No disappearance of trans-chlordane was observed under the same conditions. All the chlorinated aromatics studied were very stable to hydrolysis.

TABLE 2. ALKYL AND AROMATIC HALIDES

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
a. CHLORINATED ALKYLS						
107-05-1	Allyl Chloride		4.6E-4		63d	10
764-41-0	cis-1,4-Dichloro-2-butene		(9.1 ± 1.1)E-3		3.2d	2
110-57-6	trans-1,4-Dichloro-2-butene		(9.0 ± 0.5)E-3		3.2d	2
319-94-8	Pentachlorocychlohexene (PCCH)		3.0E-5	74 ± 3	2.1y	4
100-44-7	Benzyl Chloride		(5.1 ± 0.3)E-2		14h	4
594-20-7	2,2-Dichloropropane (2,2-DCP)		(4.7 ± 0.2)E-2		15h	4
			1.9E-2		36h	12
			2.4E-2		29h	13
72-54-8	p,p'DDD		(2.8 ± 0.9)E-6	5.2	28y	3
	1,1-Dichloroethane (1,1-DCA)		1.29E-6	4.32E-5	61y	12
58-89-9	Lindane		(1.2 ± 0.2)E-4	198 ± 6	207d	3
78-87-5	1,2-Dichloropropane		(5.0 ± 0.2)E-6	4.3E-4	15.8y	3
107-06-2	1,2-Dichlorethane (1,2-DCA)		1.1E-6		72y	12
96-18-4	1,2,3-Trichloropropane		(1.8 ± 0.6)E-6	9.9E-4	44y	2
67-72-1	Hexachloroethane			4.3E-7	1.8E9	12

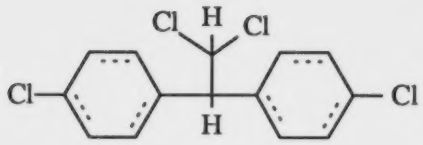
TABLE 2. ALKYL AND AROMATIC HALIDES - continued

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
b. BROMINATED ALKANES						
106-93-4	Ethylene dibromide (EDB)		9.9E-6		8y	14
126-72-7	Tris-(2,3-dibromopropyl)-phosphate (Tris)		(1.0 ± 1.1)E-5	78	4.4y	3
92-12-8	1,2-Dibromo-3-chloropropane (DBCP)			20.6	38y	2
c. BIFUNCTIONAL CHLOROALKANES						
142-28-9	1,3-Dichloropropane (1,3-DCP)		3.5E-5	1E-3	2.3y	12
96-23-1	1,3-Dichloro-2-propanol (1,3-DCA)		(3.1 ± 0.2)E-3	850 ± 87	9.1d	2
616-23-9	2,3-Dichloro-1-propanol (2,3-DCA)		(5.3 ± 0.8)E-5	20.6 ± 2.2	1.4y	2
542-76-7	3-Chloropropanenitrile		(1.3 ± 0.1)E-4	12,071 ± 1,960	22d	3
111-44-4	bis-Dichloroethylether (DCE)		(2.6 ± 0.1)E-5		3.0y	3
628-89-7	2-(2-Chloroethoxy)ethanol (CEE)		(3.2 ± 0.1)E-5		2.5y	4
107-07-3	2-Chloroethanol (2-CE)		4.5E-6	36	9.8y	4
75-00-3	Ethyl chloride		4.5E-5		1.8y	15
107-30-2	Chloromethyl methylether		21		2 min	20

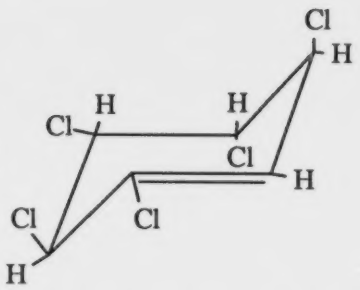
TABLE 2. ALKYL AND AROMATIC HALIDES - continued

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
d. POLYCYCLIC AND AROMATIC HALOGENATED HYDROCARBONS						
60-57-1	Dieldrin		(7.5 ± 3.3)E-6		10.5y	2
28291-10-3	DL-trans-4-Chlorostilbene Oxide	1080 ± 108	(61 ± 7.2)E-4		112h	4, 16
309-00-2	Aldrin		(3.8 ± 2.3)E-5		760d	2
465-73-6	Isodrin		1.7E-6		46y	3
5103-74-2	Cis-Chlordane			4.3E-3	>184,000	3
5103-71-9	trans-Chlordane	zero hydrolysis after 5 days at 85°C, pH 11				
108-90-7	Chlorobenzene[a]			<0.9	>900y	4
95-50-1	1,2-Dichlorobenzene[a]			<0.9	>900y	4
541-73-1	1,3-Dichlorobenzene[a]			<0.9	>900y	4
106-46-7	1,4-Dichlorobenzene[a]			<0.9	>900y	4
24009-05-0	1-Hydroxychlordene[b]			<1 X 10-4	200,000y	4
608-93-5	Pentachlorobenzene[a]			<0.9	>900y	4
95-94-3	1,2,4,5-Tetrachlorobenzene[a]			<0.9	>900y	4
88-06-2	2,4,6-Trichlorophenol[c]		(2.3 ± 3.5)E-7		>300y	4
101-14-4	4,4-Methylene-bis-(2-Chloroaniline)		<9E-8		>800y	2

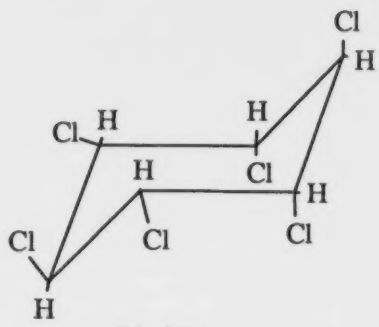
a. Based on assumed base mediated 1% disappearance after 16d at 85°C and pH 9.70 (pH 11.26 at room temperature).
b. Based on assumed base mediated 5% disappearance after 48d at 85°C and pH 9.71 (pH 11.04 at room temperature).
c. Based on assumed 5% disappearance after 330 hr at 85°C.



p,p'-DDD



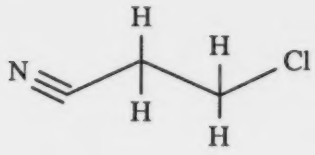
Pentachlorocyclohexene (PCCH)



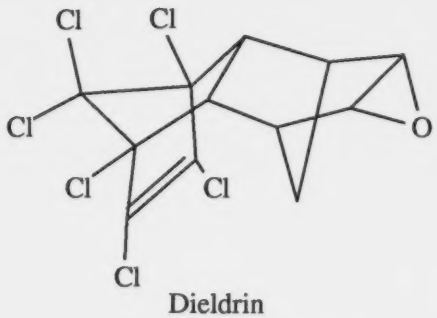
Lindane

$(Br\text{-}CH_2\text{-}CHBr\text{-}CH_2\text{-}O)_3\text{-}P = O$

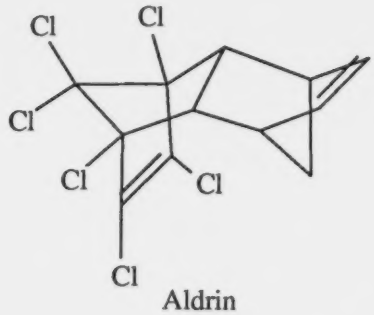
Tris(2,3-dibromopropyl)phosphate



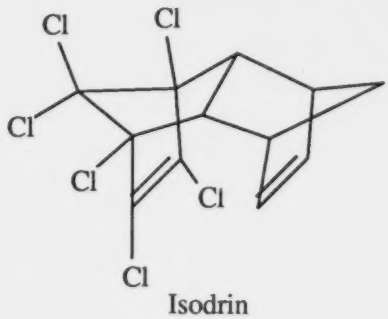
3-Chloropropanenitrile



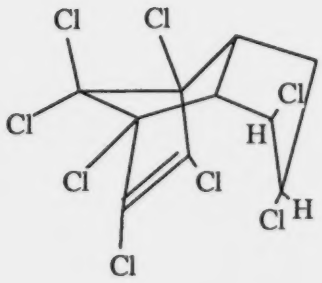
Dieldrin



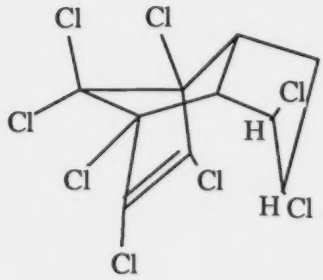
Aldrin



Isodrin



cis-Chlordane



trans-Chlordane

Figure 2. Alkyl and Aromatic Halides

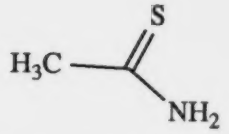
4.3 Amides (Primary and N-Substituted)

Amides generally hydrolyze by acid- and base-mediated processes to carboxylic acids and amines. When the rates determined at pH's 3 and 7 or pH's 11 and 7 were the same, the rate was reported as the neutral rate constant.

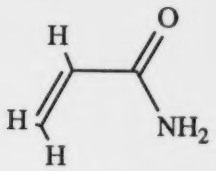
Table 3 summarizes the rate data at pH 7 and 25°C for several primary and N-substituted amides. Thioacetamide illustrates the instability introduced when sulfur is substituted for oxygen. (Acetamide is the oxygen analog.) Electronegative substituents (fluoro- and chloroacetamide) or substitutients that delocalize the carbonyl electrons (acrylamide) enhance reactivity of the amide. Pronamide hydrolysis also is enhanced by the delocalization of electrons into the dichlorophenyl substituent.

TABLE 3. PRIMARY AND N-SUBSTITUTED AMIDES

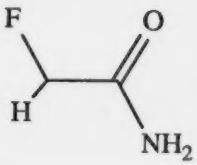
CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
a. PRIMARY						
62-55-5	Thioacetamide	(6.0 ± 0.06)E-2	(8.6 ± 1.1)E-5	1.4 ± 0.09	336d	3
60-35-5	Acetamide	3.0E-2		0.17	3,440y	10
640-19-7	2-Fluoroacetamide		(3.3 ± 0.3)E-5		2.4y	3
79-07-2	2-Chloroacetamide	4.0E-2		540	1.5y	10
79-06-1	Acrylamide	<3.6E-3	<(2.1 ± 2.1)E-6		>38y	2
b. N-SUBSTITUTED						
23950-58-5	Pronamide	4.3E-3	<1.5E-5	7.4E-2	>5y	2
591-08-2	N-(aminothioxomethyl)acetamide		(1.7 ± 0.2)E-5	1.5 ± 0.09	4.6y	3
53-96-3	2-Acetylaminofluorene		2.3E-6	6E-3	34y	3



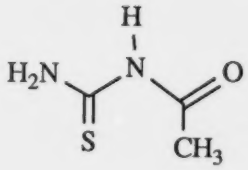
Thioacetamide



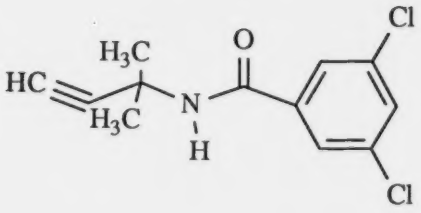
Acrylamide



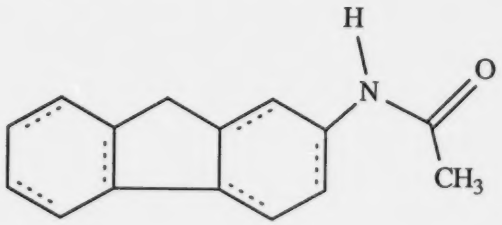
2-Fluoroacetamide



N-(Aminothioxomethyl)-Acetamide



Pronamide



2-Acetylaminofluorene

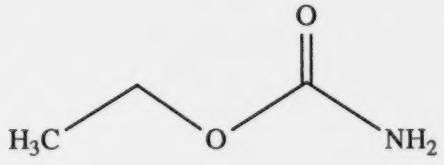
Figure 3. Primary and N-Substituted Amides

4.4 Carbamates

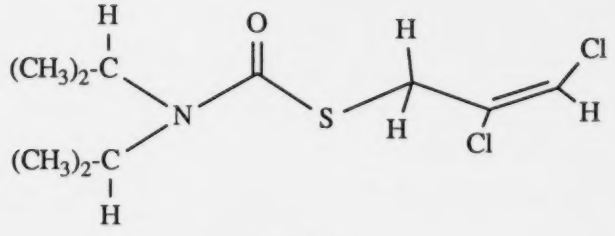
Hydrolysis of carbamates proceeds by acidic, basic, or neutral processes to give alcohols, amines, and carbon dioxide. Half-lives of carbamates as illustrated in Table 4 vary from seconds to centuries (10). Mitomycin C contains among its functional groups a carbamate, an aziridine, and a labile methoxy group. The rate limiting step in disappearance of mitomycin C is expulsion of the methoxide prior to opening of the aziridine ring (22, 23). The half-life of mitomycin C is comparable to 2-methylaziridine in Table 11. Ethyl carbamate, contrary to most carbamates, is not N-substituted. The reactivity of ethyl carbamate is comparable to the simple alkyl amides.

TABLE 4. CARBAMATES

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
50-07-7	Mitomycin C	4320	1.8E-3	43	12.9d	22, 23
51-79-6	Ethyl Carbamate		<2.6E-7	1.1E-1	>300y	2
2303-16-4	Diallate		(1.2 ± 0.7)E-5	0.9 ± 0.4	6.6y	3



Ethyl carbamate



trans-Diallate

Figure 4. Carbamates

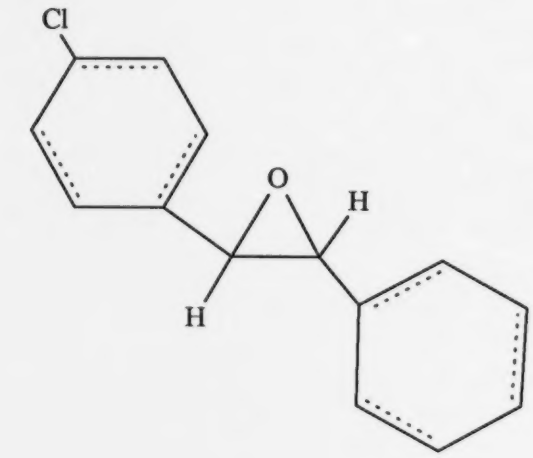
4.5 Epoxides

Hydrolysis of epoxides in acid, neutral or base catalyzed reactions yields diols as the final product. Epoxides are reactive compounds with half-lives generally minutes to less than 15 days (10), see Table 5. Aromatic or conjugated epoxides tend to be more reactive than strictly aliphatic epoxides. Acid-catalyzed hydrolysis is sensitive to the stability of the transient carbonium ion formed by protonation of the oxirane ring and subsequent breaking of one of the carbon-oxygen bonds. This enhanced reactivity is reflected in the hydrolysis rate constant of D,L-<u>trans</u>-4-chlorostilbene oxide (CSO). The stability of Dieldrin is possibly due to shielding of the oxirane group from attack by water and to lower reactivity of alkyl epoxides.

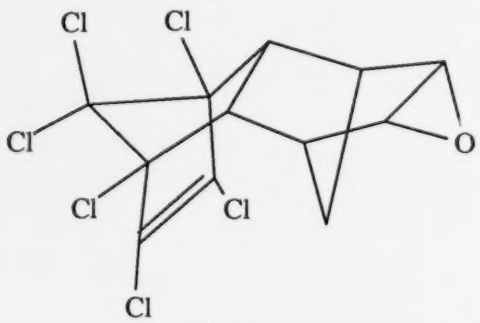
TABLE 5. EPOXIDES

CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
28291-10-3	DL-trans-4-Chlorostilbene Oxide	1080 ± 108	(61 ± 7.2)E-4[a]		112h	4, 16
60-57-1	Dieldrin		(7.5 ± 3.3)E-6		10.5y	2

a. Neutral rate from Reference 16.



trans-4-chlorostilbene oxide



Dieldrin

Figure 5. Epoxides

4.6 Nitriles

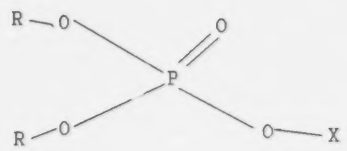
The hydrolysis of nitriles normally takes place only in the presence of either strong acids or strong bases. In both cases, amides are the first reaction products, but amides cannot be isolated as intermediates unless their rate of hydrolysis is lower than that of the parent nitrile. Nitrile data, summarized in Table 6, confirms the stability of the monofunctional alkyl nitriles (acrylonitrile and acetonitrile) under environmental conditions. Malonitrile (1,1-dicyanomethane), by comparison, is very labile to degradation even under neutral conditions. This can be attributed to the activation (ionization) of the α-hydrogens. The anion formed is unstable and some form of cleavage or hydrolysis occurs when malonitrile loses a proton to form the monoanion.

TABLE 6. NITRILES

CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
109-77-3	Malononitrile		(1.30 ± 0.40)E-3	806 ± 45	21d	3
75-05-8	Acetonitrile			5.8E-3	>130,000y	3
107-13-1	Acrylonitrile	(4.2 ± 0.3)E-2		(6.1 ± 6.5)E-1	1220y	2

4.7 Phosphate Esters

Organothiophosphate and organodithiophosphate triesters, depending on the substituents, may undergo hydronium-ion-catalyzed hydrolysis, hydroxide-ion-catalyzed hydrolysis and neutral hydrolysis and are quite reactive species. Under environmental conditions, only the neutral and hydroxide-ion-mediated hydrolyses are relevant as illustrated in Table 7. Most phosphate pesticides have the general structure:



where R = an alkyl group (usually methyl or ethyl) and X = an organic radical. Hydrolysis involves cleavage of either the P-OX (-SX) bond (hydroxide ion and neutral) or the O-X (S-X) bond (hydronium ion) depending on conditions.

When sulfur is substituted for oxygen in the P=O position, the rate of hydrolysis is decreased, whereas substitution of S for O in the P-O-X position increases the rate of hydrolysis. The greater electronegativity of the oxygen atom in the P=O(S) position enhances the positive character of the phosphorus atom and thus the attraction for the electrons on the hydroxide ion or the water molecule (17).

In breaking the P-O(S) single bond, the mercaptide anion is a better leaving group than the alkoxide. Rates of hydrolysis are therefore accelerated when S is substituted for O in this

position. The second-order alkaline hydrolysis rate constants of thioesters have been correlated to the pKa of the conjugate acid of the leaving group by the relationship:

$$\log k = m \cdot pKa + c$$

where m is the slope and c the intercept (18).

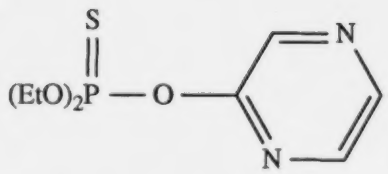
Using the m and c values from Wolfe (18), and conjugate acid pKa values calculated (9) by SPARC (2-hydroxypyrazine) or Perrin [(19) p-N,N-dimethylsulfamoyl phenol], we calculated second-order alkaline hydrolysis rate constants for O,O-diethyl-O-pyrazinyl phosphorothioate and Famphur. The calculated values in Table 7 agree within a factor of two with the laboratory-determined values. The hydrolysis of the trialkylthioester is an order of magnitude slower than the above thioesters with at least one aromatic substituent.

The greater reactivity when O is replaced by S in the leaving group is evidenced by the 50% increase in the neutral hydrolysis rate constant of O,O,S-triethyl ester over the O,O,O-triethyl ester. The reactivity of the dithioesters Phorate and Dimethoate is further enhanced by reactive groups in the alkyl side chain to yield half-lives of less than five days compared to a half-life of 115 days for Famphur.

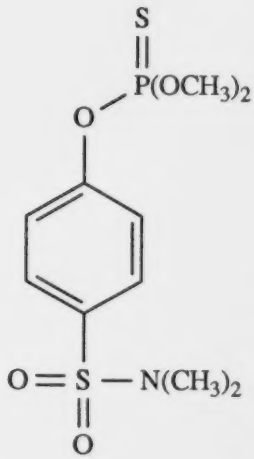
TABLE 7. PHOSPHATE ESTERS

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
a. THIOESTERS						
297-97-2	O,O-Diethyl-o-pyranzinyl phosphorothioate		(1.0 ± 0.1)E-3	7.3 ± 0.7 3.8[a]	29d	3 calculated[a]
52-85-7	Famphur		(2.5 ± 0.9)E-4	5.0 8.6[a]	115d	2 calculated[a]
126-68-1	O,O,O-Triethylester phosphorothioic acid		(2.0 ± 0.2)E-5		3.9y	3
b. DITHIOESTERS						
298-02-2	Phorate		7.2E-3		96h	3
60-51-5	Dimethoate		1.7E-4	756	118h	3
298-04-4	Disulfoton		(2.8 ± 0.4)E-4	5.99	103d	2
2524-09-6	O,O,S-Triethylester phosphorodithioic acid		(3.0 ± 0.2)E-5	1.0E-2	2.6y	3

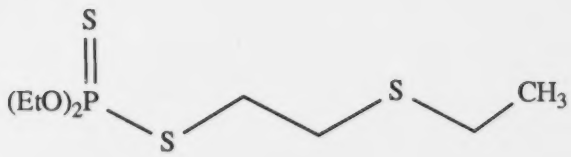
a. Calculated by the equation of Wolfe in Reference 18.



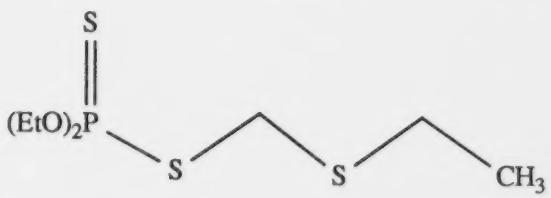
O,O-Diethyl-O-pyrazinyl
phosphorothioate



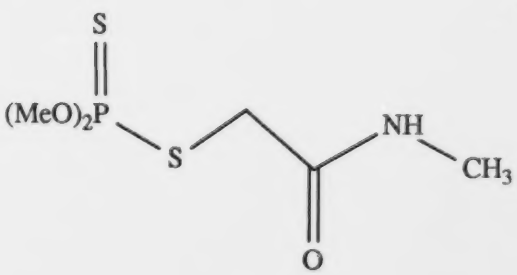
Famphur



Disulfoton



Phorate

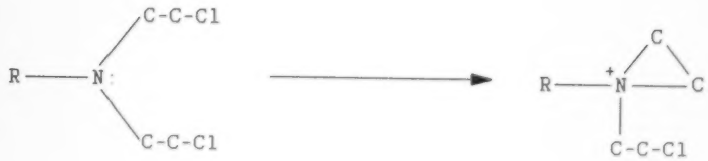


Dimethoate

Figure 6. Phosphate Esters

4.8 Alkylating Agents

The four alkylating agents are all nitrogen mustards with the general structure I,



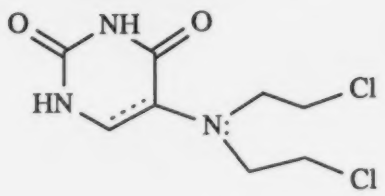
I II

where R is a substitutent that modifies reactivity. The rate determining step in aqueous solutions is formation of the highly reactive ethyleneimmonium ion II. The factor of five decrease in reactivity of chlornaphazine compared to cyclophosphamide is most likely due to the delocalization of the free pair of nitrogen electrons over the phosphamide ring, slowing the rate determining formation of the ethyleneimonium ion (Table 8, Figure 7).

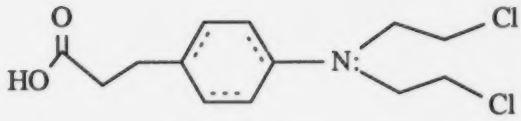
Uracil mustard (Figure 7) on the other hand is approximately three orders of magnitude more reactive than cyclophosphamide.

TABLE 8. ALKYLATING AGENTS

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
66-75-1	Uracil mustard		0.57 ± 0.08	(2.05 ± 0.2)E5	1.2h	2
305-03-3	Chlorambucil		0.40		1.7h	3
148-82-3	Melphalan		0.15		4.6h	3
494-03-1	Chlornaphazine		3.2E-3		216h	3
50-18-0	Cyclophosphamide		7.1E-4		41d	3



Uracil Mustard



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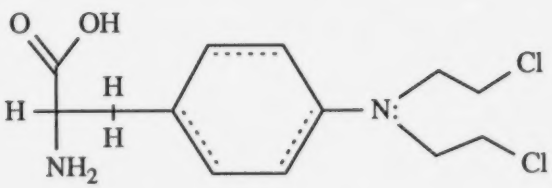

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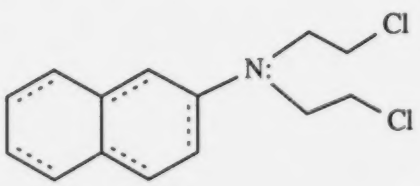

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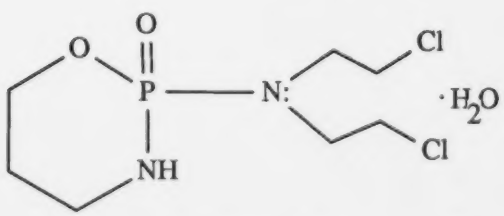


Cyclophosphamide

Figure 7. Alkylating Agents

4.9 Halogenated Ethers

The halogenated ethers were discussed in the section on bifunctional chloroalkanes (Section 4.2C). The chloromethyl ethers are orders of magnitude more reactive than ethers that have two or more carbons interspersed between the chlorine and oxygen (Table 9). The 2-(2-chloroethoxy)ethanol is a product of hydrolysis of bis-dichloroethyl ether but due to its larger hydrolysis rate constant the concentration of 2-(2-chloroethoxy) ethanol will remain low.

TABLE 9. HALOGENATED ETHERS

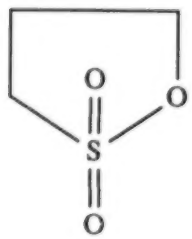
CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
107-30-2	Chloromethyl methyl ether		21		2 min	2
111-44-4	bis-Dichloroethyl ether		(2.6 ± 0.1)E-5		3.0y	4
628-89-7	2-(2-Chloroethoxy)ethanol		(3.2 ± 0.1)E-5		2.5y	4

4.10 Oxidized Sulfur Compounds

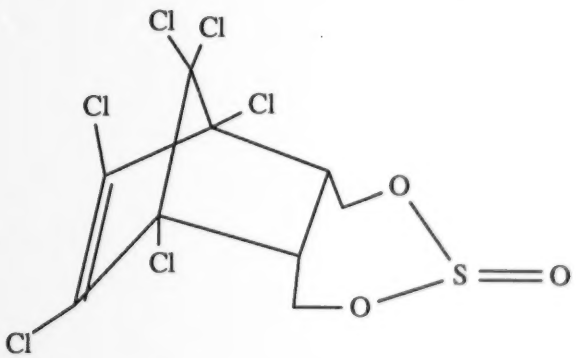
The oxidized sulfur containing compounds in Table 10 are all highly reactive. It is of intrest that the hydrolysis rate constants of the exo (Endosulfan I) and endo (Endosulfan II) isomers of Endosulfan, for practical purposes, are identical.

TABLE 10. OXIDIZED SULFUR COMPOUNDS

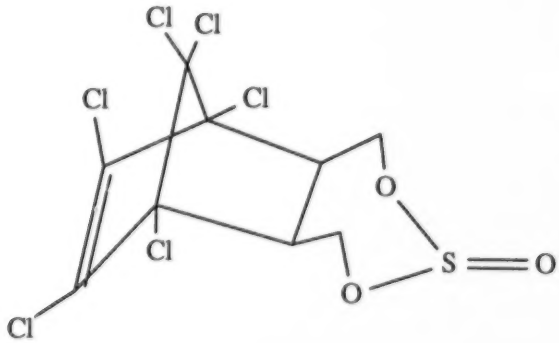
CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
77-78-1	Dimethylsulfate		0.6		1.2 min	10
1120-71-4	1,3-Propane Sultone		8.2E-2		8.5h	3
959-98-8	Endosulfan I	(8.1 ± 2.7)E-3	(3.2 ± 2.0)E-3	(1.0 ± 0.7)E4	165h	2
33213-65-9	Endosulfan II	(7.4 ± 3.9)E-3	(3.7 ± 2.0)E-3	(1.5 ± 0.9)E4	133h	2
62-50-0	Ethyl methanesulfonate		1.5E-2		46h	3



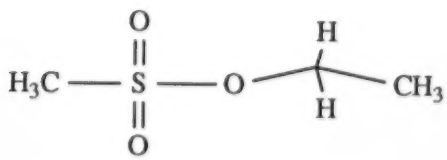
1,3-Propane Sultone



Endosulfan I



Endosulfan II



Ethyl methanesulfonate

Figure 8. Oxidized Sulfur Compounds

4.11 Other Miscellaneous Compounds

The half-lives of the pyrophosphates and nitroso compounds in Table 11 are so short, PRC discussions are meaningless. Ethylene-bis-(cithiocarbamic acid), 2,4-dithiobiuret, auramine, azaserine, daunomycin, methylthiouracil, nitroglycerine, warfarin, fluoroacetic acid sodium salt, and octamethylpyrophosphoramide lack sufficient data for PRC discussion. With the exception of α-naphthylthiourea, thiourea and its substituted analogs are resistant to hydrolysis. Possibly the stability of the resulting α-napthylamine enhances hydrolysis of α-napthylthiourea. The rate constants reported for chlorinated aromatics in part d of Table 2 make the reported hydrolysis rate constants for pentachloronitrobenzene and β-chloronaphthalene suspect.

TABLE 11. MISCELLANEOUS COMPOUNDS

CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
126-99-8	2-Chloro-1,3-butadiene		Polymerizes in absence of inhibitors			3
759-73-9	N-Nitroso-N-ethylurea		0.19	5.3E6	0.96h	3
107-49-3	Tetraethyl pyrophosphate		9.3E-2		7.5h	3
757-58-4	Hexaethyl pyrophosphate		9.3E-2		7.5h	3
70-25-7	N-Methyl-N-nitro-N-nitrosoguanidine		2.7E-2	9.5E4	19h	3
615-53-2	N-Nitroso-N-methylurethane		2.9E-2	2.9E3	24h	3
111-54-6	Ethylene-bis(dithiocarbamic acid)	848	0.01		69h	3
50-07-7	Mitomycin C	4320	1.8E-3	4.30	12.9d	22, 23
75-55-8	2-Methylaziridine		8.0E-3		87h	3
541-53-7	2,4-Dithiobiuret		7.1 ± 1.3E-3		98h	3
492-80-8	Auramine		3.9E-4		74d	3
115-02-6	Azaserine	328 ± 20	2.6 ± 0.4E-4	6.8 ± 0.7	99d	3
20830-81-3	Daunomycin		9.7 ± 0.5E-5	10	298d	3
86-88-4	α-Naphthylthiourea		8.0 ± 2.4E-5	9.9E2	361d	3
82-68-8	Pentachloronitrobenzene		2.8 ± 0.7E-5		2.8y	2
56-84-2	Methylthiouracil		9.7 ± 2.7E-6		8.2y	3

TABLE 11. MISCELLANEOUS COMPOUNDS - continued

CAS Number	Compound	Rate Constants (25°C) Acid $M^{-1} hr^{-1}$	Neutral hr^{-1}	Base $M^{-1} hr^{-1}$	Calculated Half-Life pH 7, 25°C	Ref.
91-58-7	β-Chloronaphthalene		9.5 ± 2.8E-6		8.3y	3
55-63-0	Nitroglycerine			77 ± 11	10y	2
81-81-2	Warfarin	1.4E-4	4.9E-6	0.026	16y	2
62-74-8	Fluoroacetic acid, sodium salt		<1.7E-6		>47y	2
5344-82-1	1-(o-Chlorophenyl)thiourea		(9.8 ± 3.0)E-7	0.14 ± 0.03	81y	3
62-56-6	Thiourea		<5.3E-7		>150y	2
152-16-9	Octamethylpyrophosphoramide	0.23 ± 0.03		1E-4	3,400y	3
96-45-7	Ethylene thiourea	zero hydrolysis within experimental error after 90 days at 90°C and pHs 3, 7, and 11				3

Predictive Techniques

Table 12 contains second-order alkaline hydrolysis rate constants that were either determined from laboratory measurements (3, 11, 10, and 21), computer-estimated based on fundamental molecular properties (9, SPARC) or correlation with infrared spectra (8, Collette), or calculated using a simple regression equation based on electronic and steric parameters (7). Where measured values were available for comparison, SPARC generally predicted a higher value and Collette's correlation a lower value but both were generally within a factor of two of the measured value.

The greater reactivity of methyl esters in comparison with the corresponding ethyl esters is seen (Table 12) in the values for three methyl-ethyl pairs. SPARC lacked the parameters needed to calculate a rate for the 2,4-D methyl ester containing the phenoxy substituent. A methyl substituent on the β-carbon of α,β-unsaturated esters retards hydrolysis compared to a methyl on the α-carbon. The β-carbon methyl apparently strengthens the inductive π electron resonance with the carbonyl carbon and retards attack by the negatively charged hydroxyl ion. Steric hindrance by the methyl on the α-carbon is not a factor due to the planar orientation of substituents on the double bond.

Figure 9 is a SPARC-generated pH-rate profile for methyl methacylate. This allows calculation of k_h at any pH.

TABLE 12. PREDICTED AND LABORATORY DETERMINED HYDROLYSIS RATE CONSTANTS OF CARBOXYLATE ESTERS

CAS Number	Compound	Rate Constants (25°C) Acid M^{-1} hr^{-1}	Neutral hr^{-1}	Base M^{-1} hr^{-1}	Calculated Half-Life pH 7, 25°C	Ref.
80-62-6	Methyl methacrylate[a]			200 ± 47[b]	3.9y	3
				279	2.8y	9*
				70	11.3y	8**
	Ethyl methacrylate			185	4.3y	9*
96-33-3	Methyl acrylate			408[b]	1.9y	11
	Ethyl acrylate			210[b]	3.8y	11
	trans-Ethyl crotonate[c,d]			47[b]	16.8y	21
				86	9.2y	9*
				10.9	72y	7***
	trans-Methyl crotonate			207	3.8y	9*
93-89-0	Ethyl benzoate			108[b]	7.3y	10
				134	5.9y	9*
1928-38-7	2,4-D-Methyl ester			41,000 ± 5,000[b]	7d	4
				26,080	11d	8**

a. Methyl 2-methylacrylate.
b. Determined in the laboratory.
c. Ethyl 3-methylacrylate
d. Halonen also reported an identical rate for the cis iscmer.

* SPARC
** Collette
*** Drossman et al.

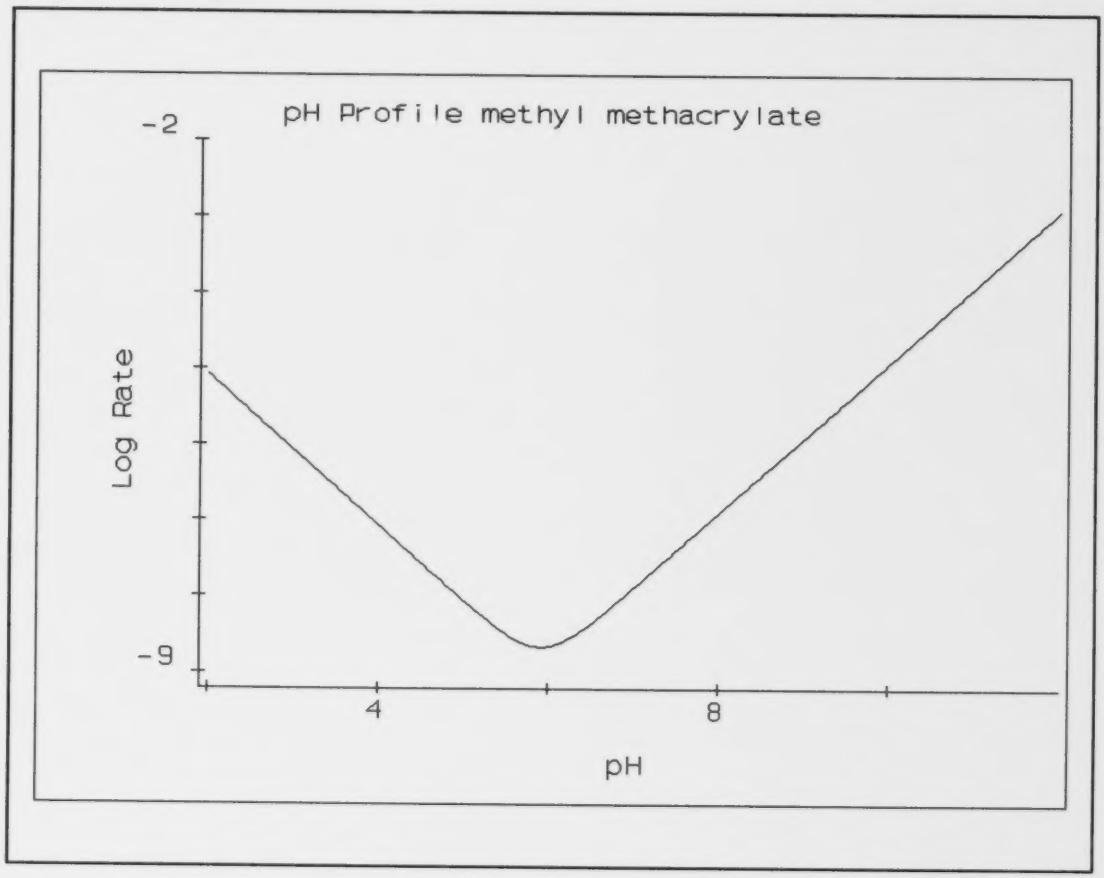


Figure 9. SPARC Generated pH-rate Profile of Methyl Methacrylate

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